Total Synthesis of Advanced Iboga Congeners

European Ibogaine Forum 2018

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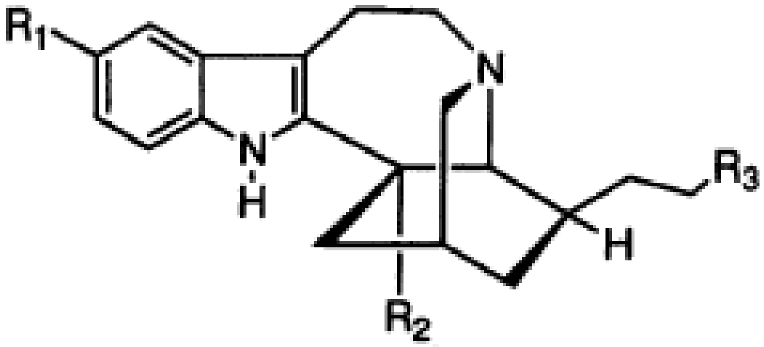
CENTRAL AMERICA HEALTH SCIENCES UNIVERSITY
BELIZE MEDICAL COLLEGE

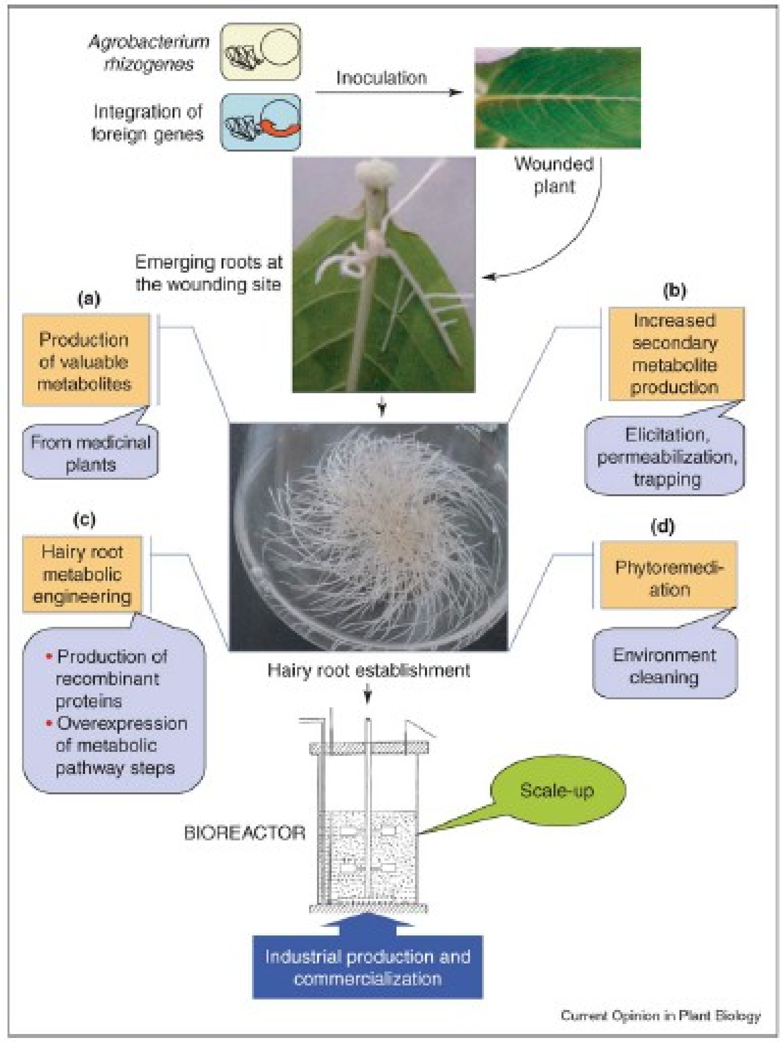


1 $R_1 = OCH_3$, $R_2 = H$, $R_3 = H$, ibogaine
2 $R = H$, $R_2 = CO_2CH_3$, $R_3 = H$, coronaridine
3 $R_1 = H$, $R_2 = CO_2CH_3$, $R_3 = OCH_3$, 18-methoxycoronaridine

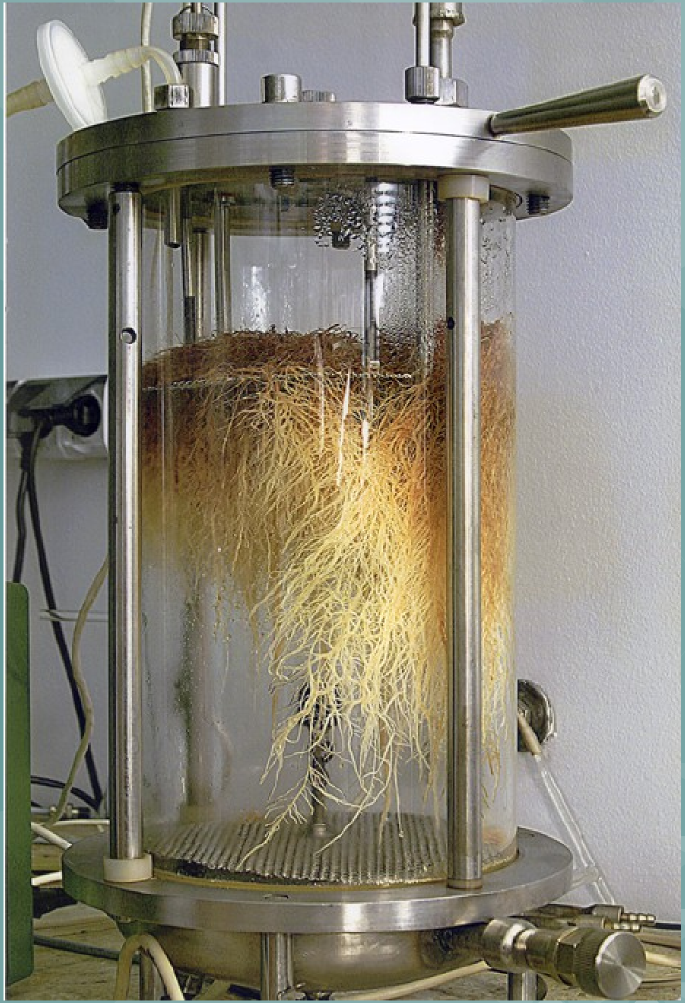
Figure 1. Compounds with established antiaddiction activity.

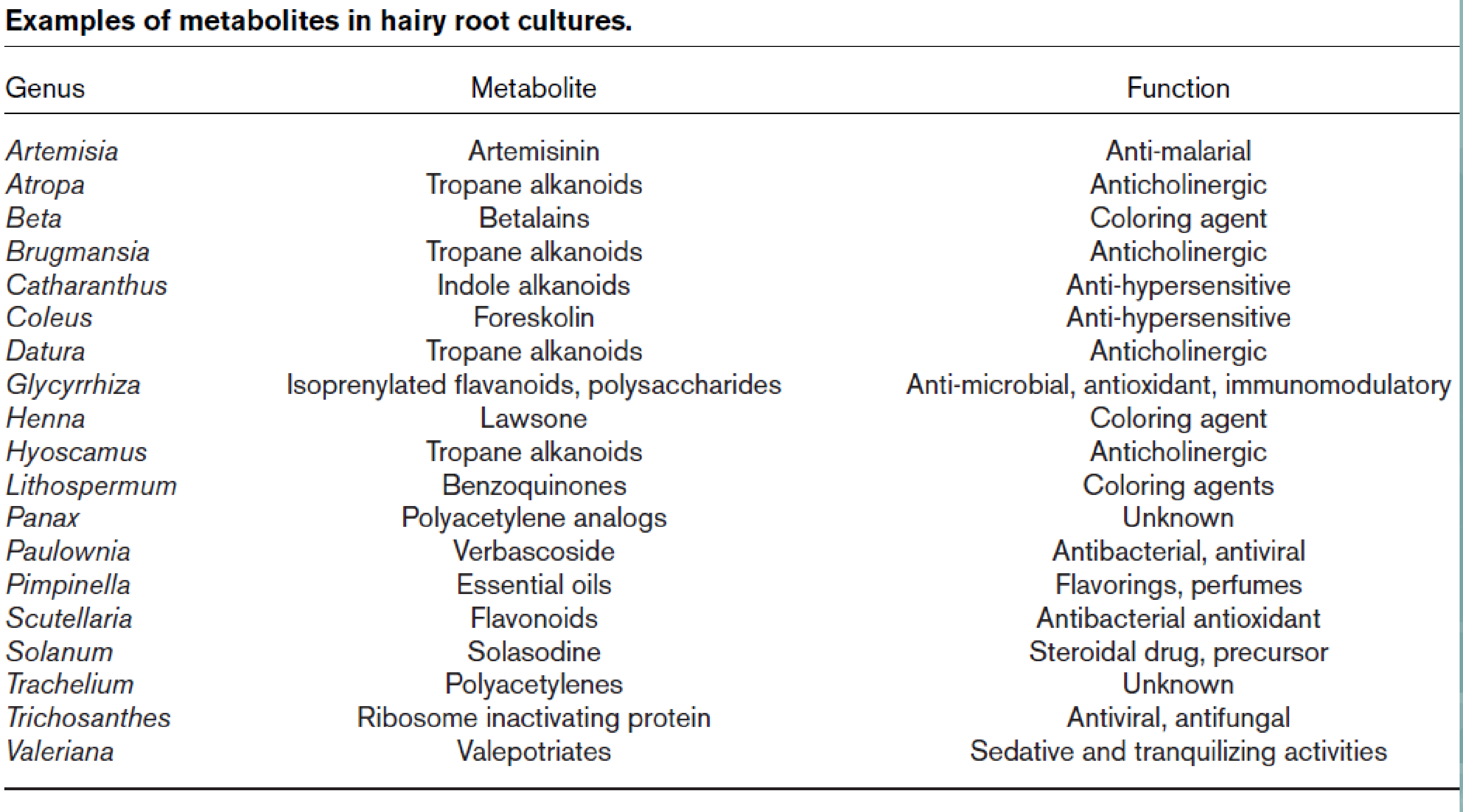
KRONOS
Shish
Breakfas
Lunch
Dinner
Catering
Take-ou

RM5


Agrobacterium rhizogenes
Integration of foreign genes
Inoculation
Wounded plant
Emerging roots at the wounding site
(a)
Production of valuable metabolites
From medicinal plants
(b)
Increased secondary metabolite production
Elicitation, permeabilization, trapping
(c)
Hairy root metabolic engineering
• Production of recombinant proteins
• Overexpression of metabolic pathway steps
(d)
Phytoremedi-ation
Environment cleaning
Hairy root establishment
BIOREACTOR
Scale-up
Industrial production and commercialization

Current Opinion in Plant Biology

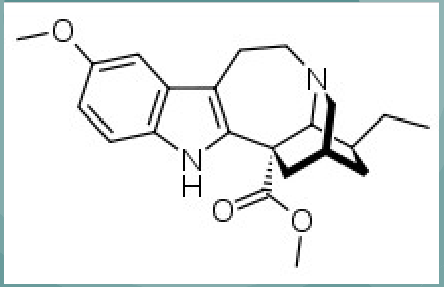




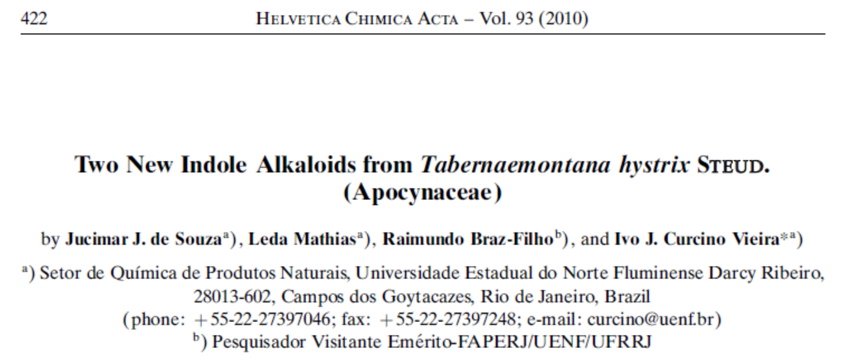
Examples of metabolites in hairy root cultures.

Genus	Metabolite	Function
Artemisia	Artemisinin	Anti-malarial
Atropa	Tropane alkanoids	Anticholinergic
Beta	Betalains	Coloring agent
Brugmansia	Tropane alkanoids	Anticholinergic
Catharanthus	Indole alkanoids	Anti-hypersensitive
Coleus	Foreskolin	Anti-hypersensitive
Datura	Tropane alkanoids	Anticholinergic
Glycyrrhiza	Isoprenylated flavanoids, polysaccharides	Anti-microbial, antioxidant, immunomodulatory
Henna	Lawsone	Coloring agent
Hyoscamus	Tropane alkanoids	Anticholinergic
Lithospermum	Benzoquinones	Coloring agents
Panax	Polyacetylene analogs	Unknown
Paulownia	Verbascoside	Antibacterial, antiviral
Pimpinella	Essential oils	Flavorings, perfumes
Scutellaria	Flavonoids	Antibacterial antioxidant
Solanum	Solasodine	Steroidal drug, precursor
Trachelium	Polyacetylenes	Unknown
Trichosanthes	Ribosome inactivating protein	Antiviral, antifungal
Valeriana	Valepotriates	Sedative and tranquilizing activities

Voacanga africana



Voacangine



422 Helvetica Chimica Acta – Vol. 93 (2010)

Two New Indole Alkaloids from *Tabernaemontana hystrix* Steud. (Apocynaceae)

by **Jucimar J. de Souza**[a]), **Leda Mathias**[a]), **Raimundo Braz-Filho**[b]), and **Ivo J. Curcino Vieira***[a])

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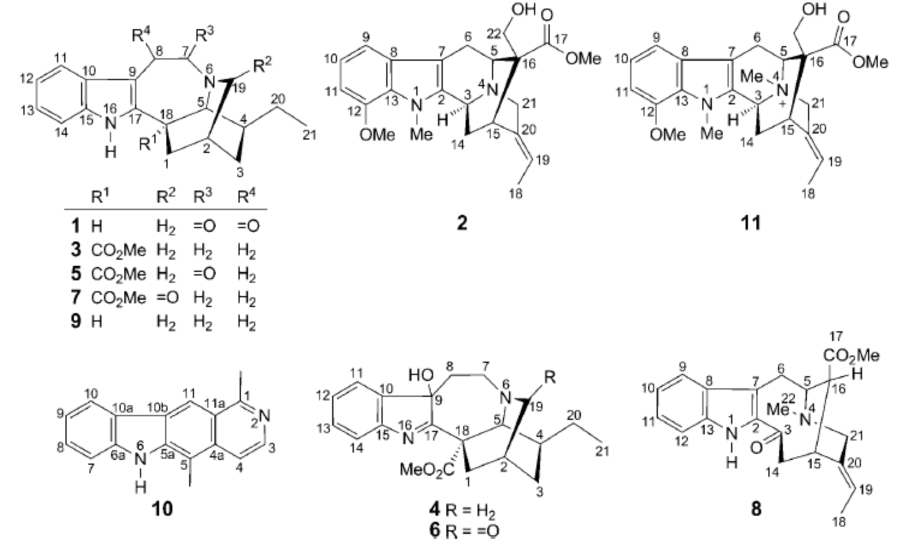
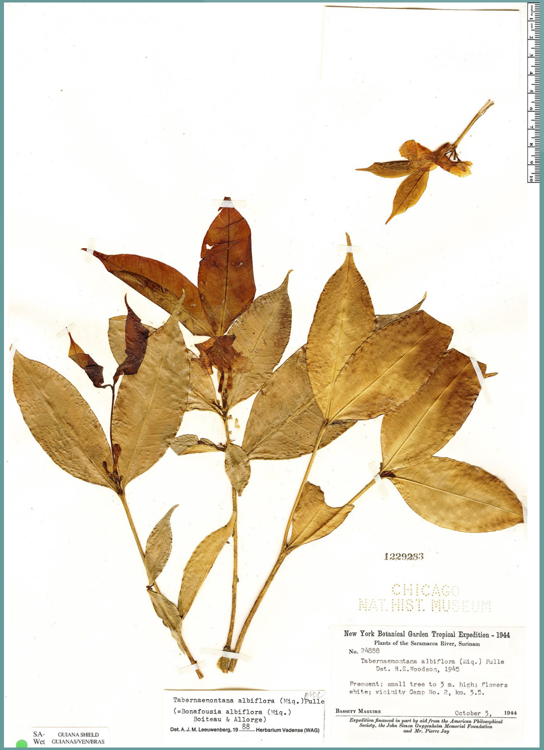
(phone: +55-22-27397046; fax: +55-22-27397248; e-mail: curcino@uenf.br)
[b]) Pesquisador Visitante Emérito-FAPERJ/UENF/UFRRJ



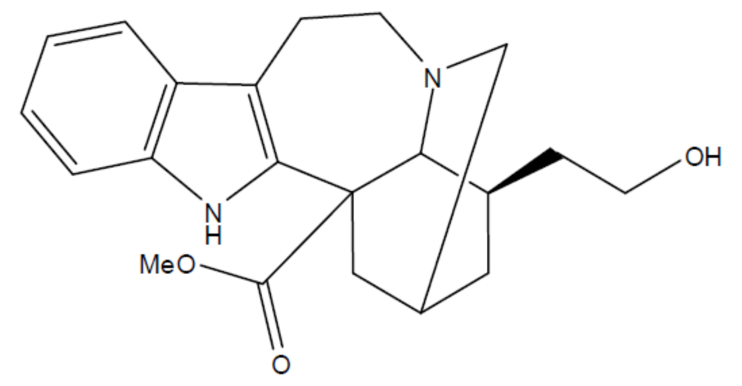
	R^1	R^2	R^3	R^4
1	H	H_2	=O	=O
3	CO_2Me	H_2	H_2	H_2
5	CO_2Me	H_2	=O	H_2
7	CO_2Me	=O	H_2	H_2
9	H	H_2	H_2	H_2

Figure. *Alkaloids isolated from* Tabernaemontana hystrix

coronaridine (3)
coronaridine hydroxyindolenine (4)
5-oxocoronaridine (5)
3-oxocoronaridine hydroxyindolenine (6
3-oxocoronaridine (7)
vobasine (8)
ibogamine (9)
olivacine (10)


1229283
CHICAGO
NAT. HIST. MUSEUM
New York Botanical Garden Tropical Expedition - 1944
Plants of the Saramacca River, Surinam
No. 24888
Tabernaemontana albiflora (Miq.) Pulle
Det. R.E.Woodson, 1945
Frequent; small tree to 3 m. high; flowers white; vicinity Camp No. 2, km. 3.5.
Bassett Maguire October 3, 1944
Expedition financed in part by aid from the American Philosophical Society, the John Simon Guggenheim Memorial Foundation and Mr. Pierre Jay
APOC
Tabernaemontana albiflora (Miq.) Pulle
(=Bonafousia albiflora (Miq.) Boiteau & Allorge)
Det. A. J. M. Leeuwenberg, 19 88 Herbarium Vadense (WAG)
SA- Wet
GUIANA SHIELD
GUIANAS/VEN/BRAS

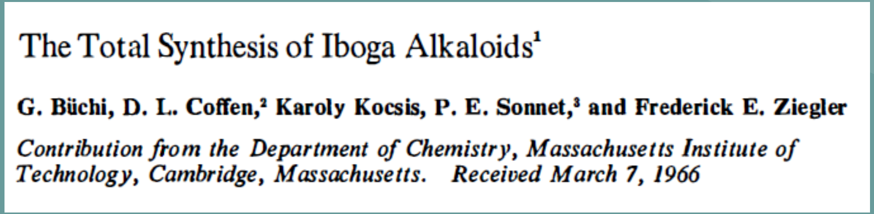
Tabernaemontana albiflora



Albifloranine

Algertza
CC BY SA

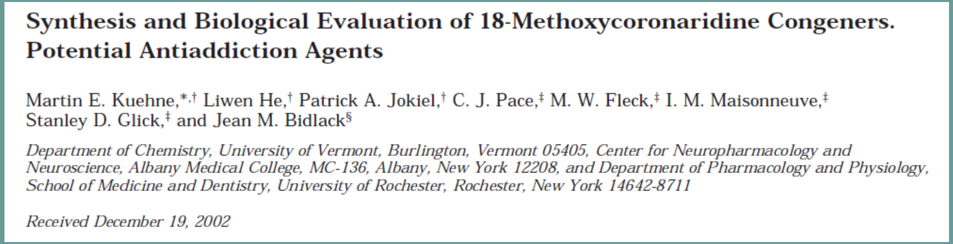
Historical Chemistry



The Total Synthesis of Iboga Alkaloids[1]

G. Büchi, D. L. Coffen,[2] Karoly Kocsis, P. E. Sonnet,[3] and Frederick E. Ziegler

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts. *Received March 7, 1966*

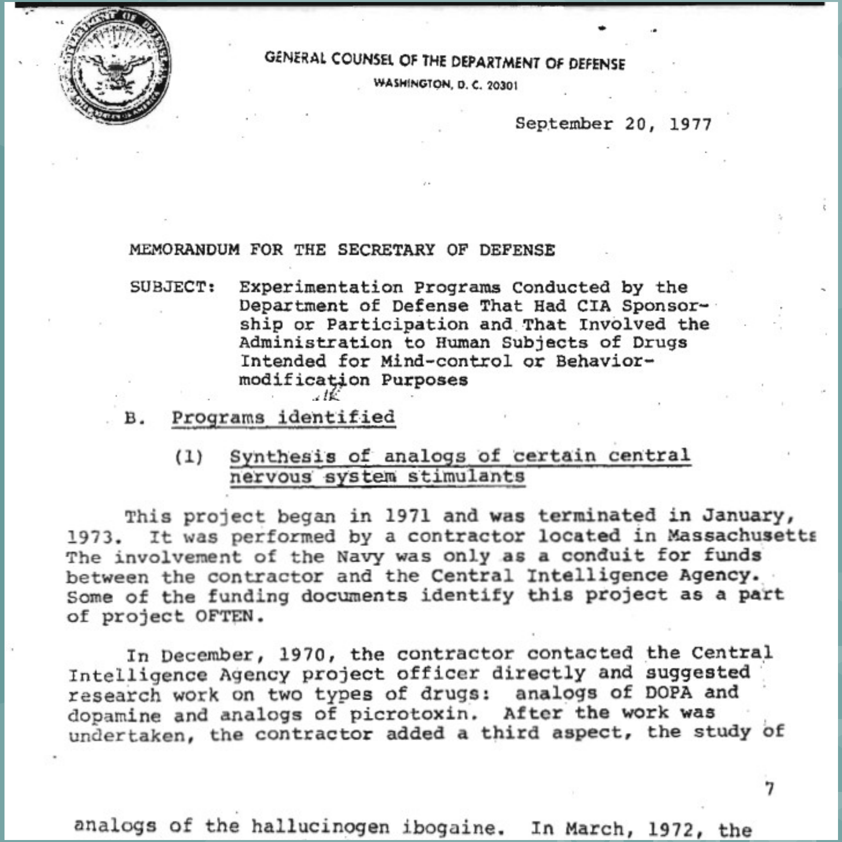


Synthesis and Biological Evaluation of 18-Methoxycoronaridine Congeners. Potential Antiaddiction Agents

Martin E. Kuehne,*,† Liwen He,† Patrick A. Jokiel,† C. J. Pace,‡ M. W. Fleck,‡ I. M. Maisonneuve,‡ Stanley D. Glick,‡ and Jean M. Bidlack§

Department of Chemistry, University of Vermont, Burlington, Vermont 05405, Center for Neuropharmacology and Neuroscience, Albany Medical College, MC-136, Albany, New York 12208, and Department of Pharmacology and Physiology, School of Medicine and Dentistry, University of Rochester, Rochester, New York 14642-8711

Received December 19, 2002



GENERAL COUNSEL OF THE DEPARTMENT OF DEFENSE
WASHINGTON, D. C. 20301

September 20, 1977

MEMORANDUM FOR THE SECRETARY OF DEFENSE

SUBJECT: Experimentation Programs Conducted by the Department of Defense That Had CIA Sponsorship or Participation and That Involved the Administration to Human Subjects of Drugs Intended for Mind-control or Behavior-modification Purposes

B. Programs identified

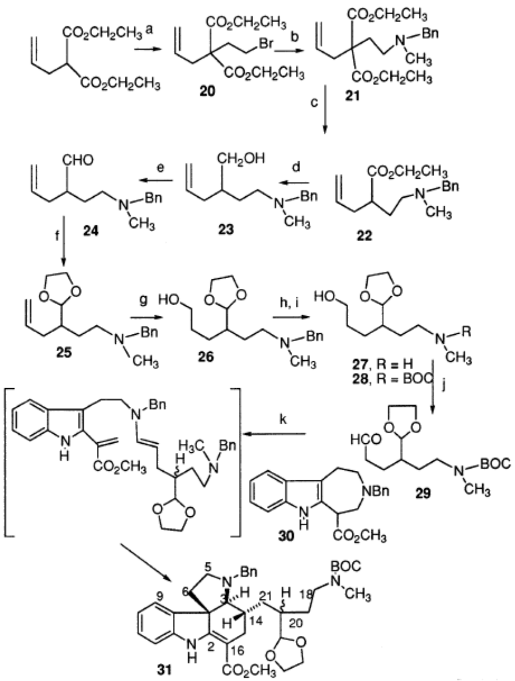
(1) Synthesis of analogs of certain central nervous system stimulants

This project began in 1971 and was terminated in January, 1973. It was performed by a contractor located in Massachusetts. The involvement of the Navy was only as a conduit for funds between the contractor and the Central Intelligence Agency. Some of the funding documents identify this project as a part of project OFTEN.

In December, 1970, the contractor contacted the Central Intelligence Agency project officer directly and suggested research work on two types of drugs: analogs of DOPA and dopamine and analogs of picrotoxin. After the work was undertaken, the contractor added a third aspect, the study of

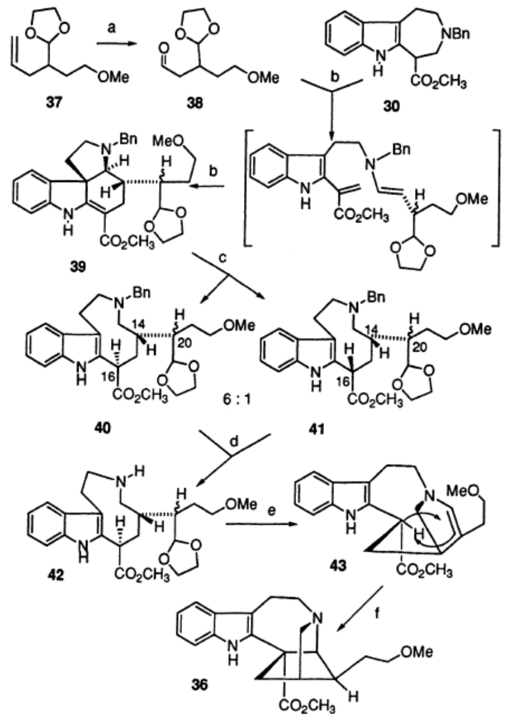
analogs of the hallucinogen ibogaine. In March, 1972, the

Scheme 2[a]



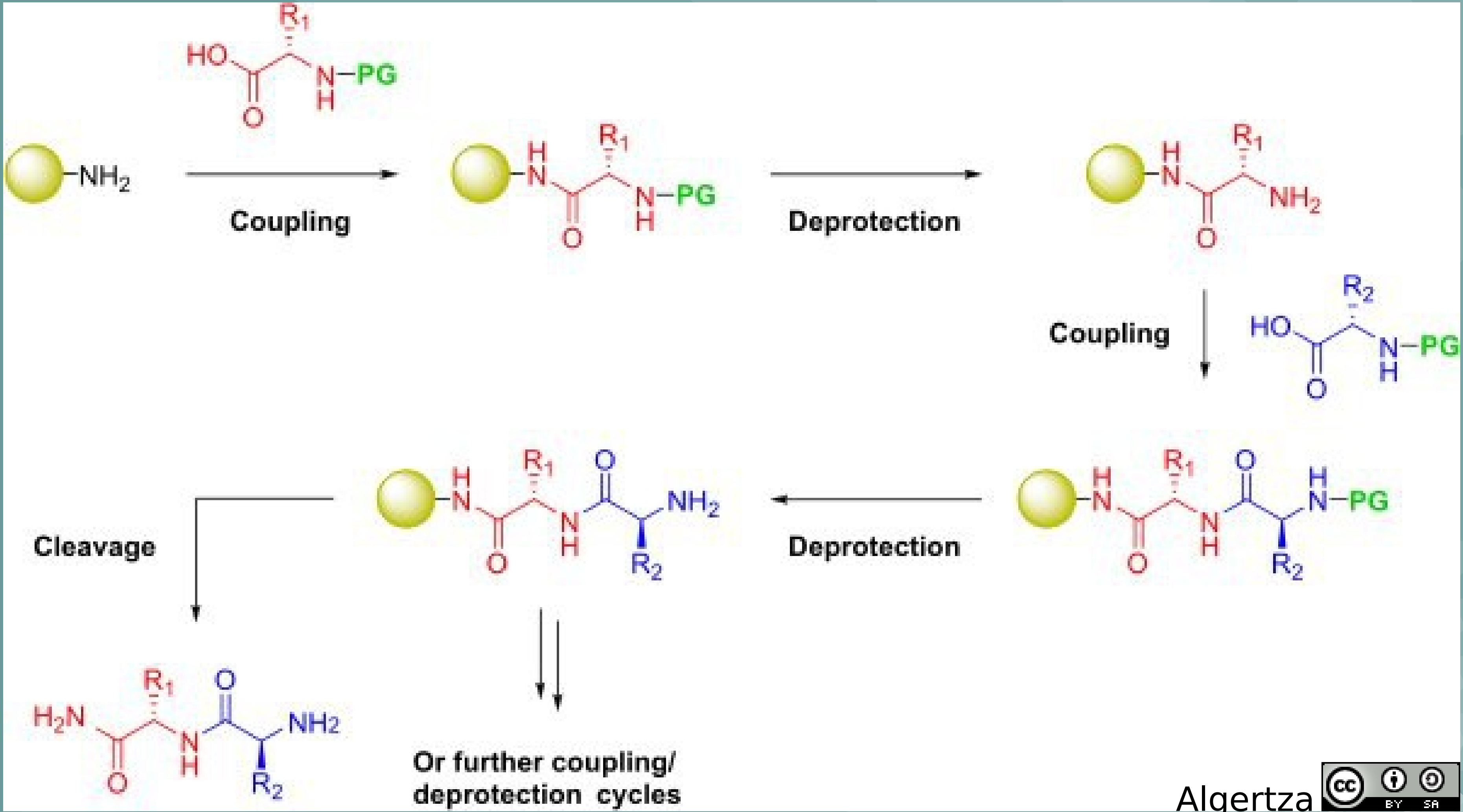
[a] Reagents and conditions: (a) NaH, THF, Br(CH$_2$)$_2$Br, 81%; (b) Me(Bn)NH, K$_2$CO$_3$, acetone, 36 h reflux, 56%; (c) LiCl, DMSO/DMF, 190 °C, 6 h, 97%; (d) LAH, ether, 98%; (e) (COCl)$_2$, DMSO, −78 °C, then Et$_3$N, −78 °C, 10 h, 92%; (f) ethylene glycol, TMSCl, CH$_2$Cl$_2$, 72 h reflux, 90%; (g) disiamylborane, THF, −10 °C, 3 h, then H$_2$O$_2$, NaOH, 95%; (h) H$_2$, Pd/C, HOAc, 79%; (i) BOC$_2$O, CH$_2$Cl$_2$, 99%; (j) (COCl)$_2$, DMSO, then Et$_3$N, 92%; (k) 135 °C, neat, 30 min, 93%.

Scheme 4[a]



[a] Reagents and conditions: (a) OsO$_4$ (cat.), NaIO$_4$, room temp, 24 h (90%); (b) neat, 130 °C, 1 h (76%); (c) NaBH$_4$, HOAc, 90 °C, 20 min (63%); (d) 10% Pd/C, H$_2$, HOAc (95%); (e) 10% HCl/CH$_3$CN, room temp, 45 min (94%); (f) toluene, reflux 24 h (64%).

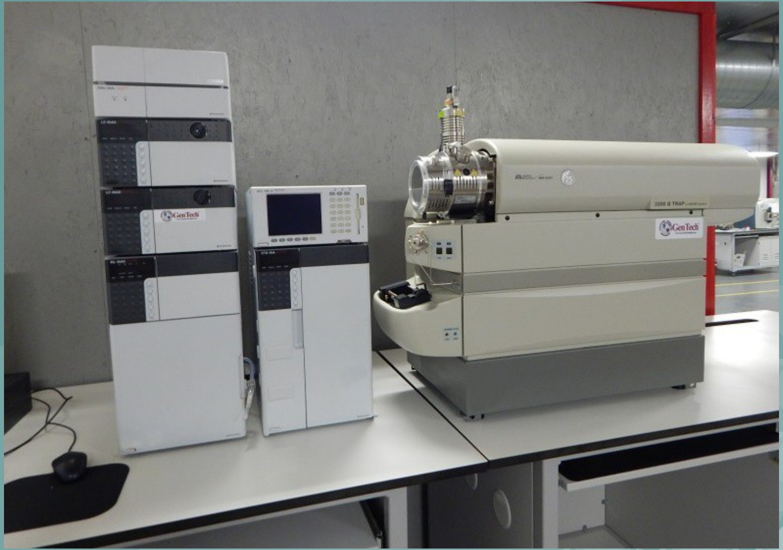
isoquinuclidine core of 18-MC (**3**) is essential for its biological activity or if a [2.2.1] bridged compound **36**

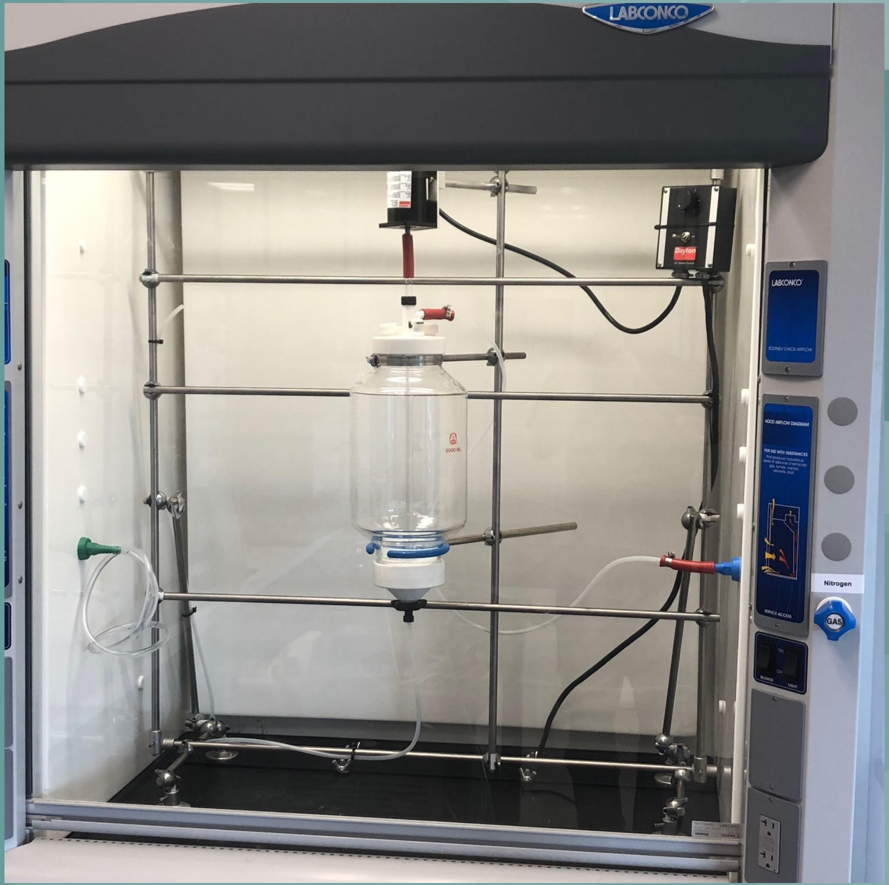


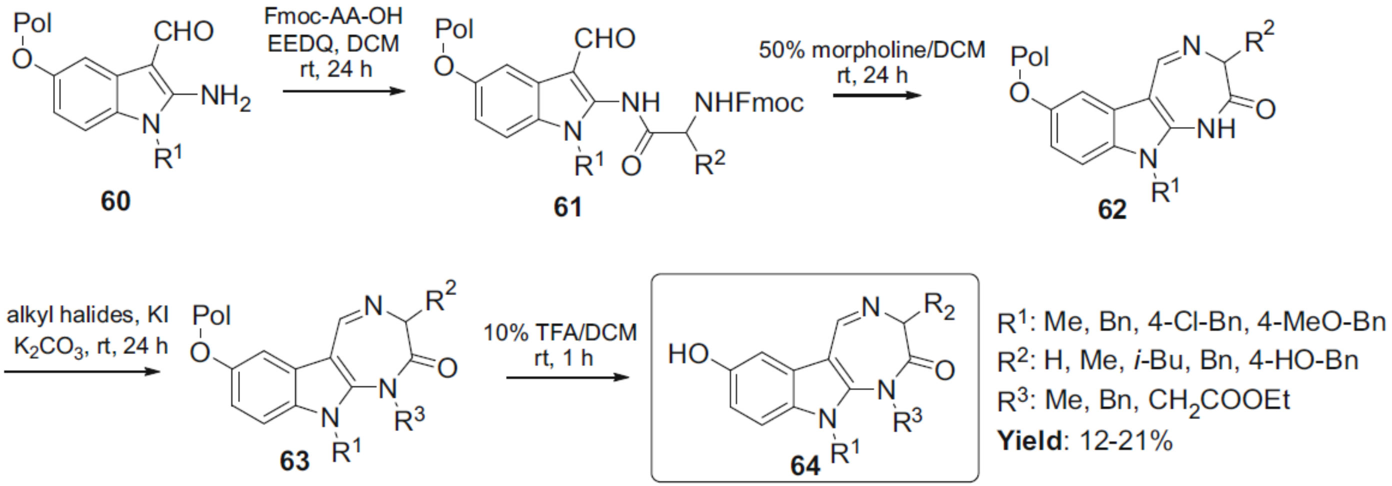
Algertza

cc BY SA

PERIODIC TABLE
Premier

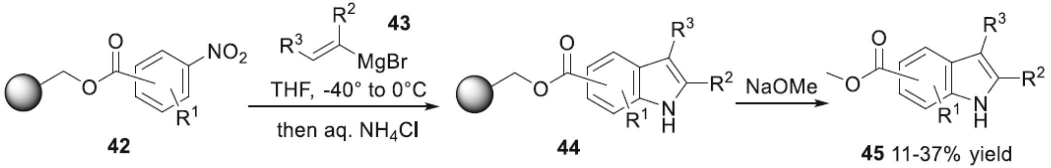

GenTech
3200 Q TRAP
GenTech


LABCONCO
Dayton
5000 ML
LABCONCO
Nitrogen
GAS

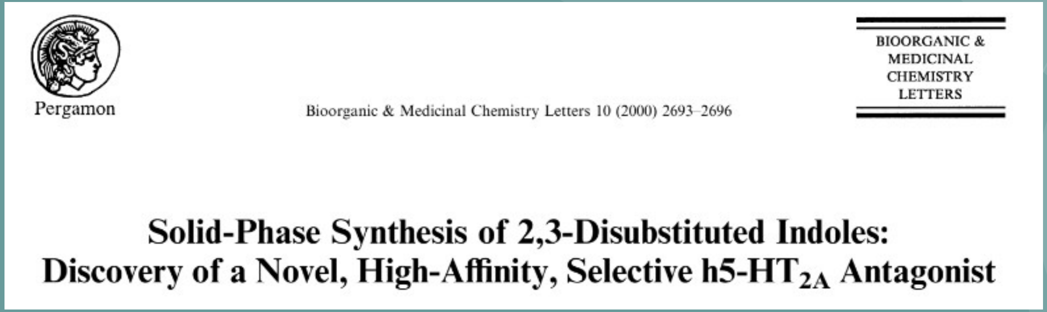


R^1: Me, Bn, 4-Cl-Bn, 4-MeO-Bn
R^2: H, Me, *i*-Bu, Bn, 4-HO-Bn
R^3: Me, Bn, CH$_2$COOEt
Yield: 12-21%

Scheme 11 Solid-phase synthesis of indole-diazepine-fused heterocycles



Scheme 15 Solid-phase indole synthesis under Bartoli procedure

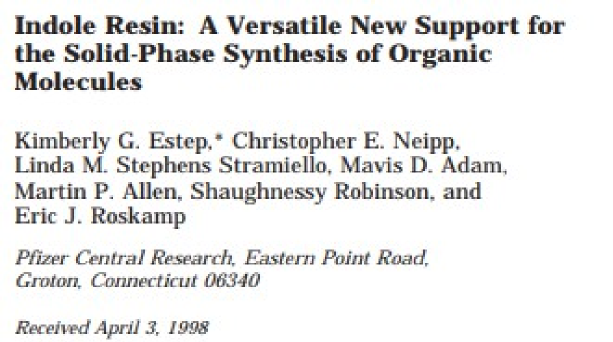


Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 2693–2696

BIOORGANIC &
MEDICINAL
CHEMISTRY
LETTERS

Solid-Phase Synthesis of 2,3-Disubstituted Indoles: Discovery of a Novel, High-Affinity, Selective h5-HT_{2A} Antagonist



Indole Resin: A Versatile New Support for the Solid-Phase Synthesis of Organic Molecules

Kimberly G. Estep,* Christopher E. Neipp,
Linda M. Stephens Stramiello, Mavis D. Adam,
Martin P. Allen, Shaughnessy Robinson, and
Eric J. Roskamp

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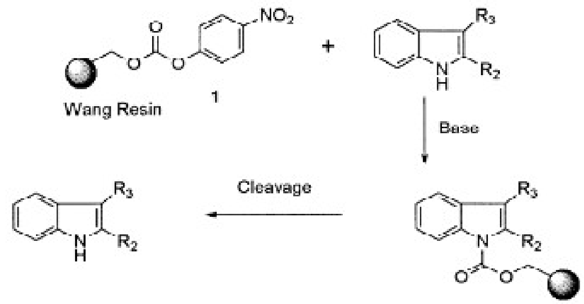
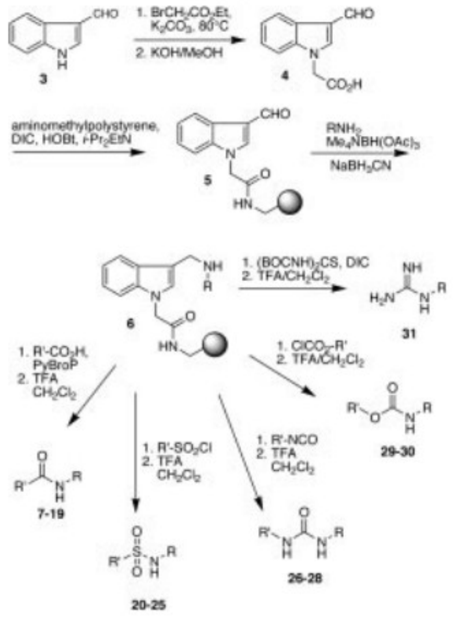
Received April 3, 1998



Scheme 1.

Scheme 1



Solid Phase Synthesis

Automated

Reaction Monitored analytically

Microwave acceleration

Process transferable